II. AMENDMENT TO THE CLAIMS

1. (Currently Amended) A process for the replication of a nucleic acid template comprising:

providing ~~said~~ a primer being bonded to a carrier macromolecule having a molecular weight in excess of 80,000 Daltons;

hybridizing the bound primer to said template; and

extending said primer to form an extended primer which ~~replicate~~ replicates said template in complementary form,

wherein said carrier macromolecule is a natural or synthetic polysaccharide, a homopolyamino acid, or a synthetic polymer having nucleophilic functional groups.

2. (Cancelled)

3. (Currently Amended) ~~A process as claimed in Claim 1,~~ A process for the replication of a nucleic acid template comprising:

providing a primer being bonded to a carrier macromolecule having a molecular weight in excess of 80,000 Daltons;

hybridizing the bound primer to said template; and

extending said primer to form an extended primer which replicates said template in complementary form,

wherein said carrier ~~macro molecule~~ macromolecule is a dextran, a starch, an hydroxyethyl-starch, an hydroxypropyl-starch, a glycogen, an agarose derivative or cellulose derivative, or a natural gum.

4. (Previously Amended) A process as claimed in claim 3, wherein the carrier macromolecule in its free state is substantially linear and substantially uncharged at a pH in the range of 4 to 10.

5. (Currently Amended) A process as claimed in claim 4, wherein said carrier molecule has a peak molecular weight in the range of in excess of 80,000 to ~~40,000,00~~ 4,000,000 Daltons.

6. (Previously Amended) A process as claimed in claim 5, wherein said carrier macromolecule is water soluble.

7. (Currently Amended) A process as claimed in claim 6, wherein said primer is bound to said carrier ~~macro-molecule~~ macromolecule via one or more moieties derived from divinyl sulphone, each of which moieties is attached to each of the carrier macromolecule and the primer by a covalent linkage formed between on of the two vinyl groups of a divinyl sulphone molecule and a reactive functionality on the carrier macromolecule or primer.

8. (Previously Amended) A process as claimed in claim 7, wherein said primer is extended by the action of polymerase incorporating nucleotides on to said primer.

9. (Currently Amended) A process as clamed in ~~Claim~~ claim 7, wherein said primer is extended in a polymerase chain reaction (pcr), strand displacement amplification (sda), self-sustained sequence replication (3sr or nucleic acid sequence-based amplification (nasba) amplification procedure.

10. (Currently Amended) A process as claimed in claim 7, wherein said primer is extended by the action of a ligase ligating said primer to at least one ~~further~~ another primer hybridised to said template.

11. (Currently Amended) A process as claimed in ~~Claim~~ claim 7, wherein said template is a double stranded template and is denatured to single stranded form, said carrier macromolecule-bound primer is complementary in sequence to a region of a first one of the template strands and a second primer is provided which is complementary in sequence to a region of the other strand, which second primer is also extended so as to form a complementary sequence copy of said template second strand.

12. (Previously Amended) A process as claimed in claim 10, wherein said carrier macromolecule is bound to a solid support.

13. (Currently Amended) A process as claimed in ~~Claim~~ claim 8, wherein a second primer is extended in said amplification procedure which is also bound to a carrier macromolecule.

14. (Currently Amended) A process as claimed in ~~Claim~~ claim 10, wherein ~~a said further~~ another primer which is ligated by said ligase is also bound to a carrier macromolecule.

15. (Previously Amended) A process as claimed in claim 14, wherein during the extension of a said primer, a detectable marker is incorporated into the extended primer.

16. (Previously Amended) A process as claimed in claim 15, wherein said extension of the primer is conducted *in situ* in a biological sample.

17. (Currently Amended) A process as claimed in ~~Claim~~ claim ~~14~~ 16, wherein said biological sample is a plant or animal tissue sample, microorganism culture, or microorganism culture medium.

18. (Currently Amended) A method of detecting the presence of a nucleic acid bound to a non-nucleotide carrier macromolecule comprising:

providing a first nucleic acid bound to a carrier macromolecule having a molecular weight in excess of 80,000 Daltons;

providing a second nucleic acid bound to a carrier macromolecule having a molecular weight in excess of 80,000 Daltons [,];

contacting said first and second nucleic acids under hybridization conditions[,]; and

detecting hybridization between said first and second nucleic acids.

19. (Currently Amended) A method of detecting the presence of a nucleic acid template sequence comprising replicating the template by a method as claimed in ~~any one of Claims 1 to 17~~ claim 17 to produce replicated template bound to a said carrier macromolecule

and detecting the presence of said replicated template bound to the carrier macromolecule by a method as claimed in claim 18.

20. (Currently Amended) A method of detecting a nucleic acid sequence comprising making a probe for detecting said sequence by using said sequence as a template sequence in a method as claimed in ~~any one of Claims 1 to 17~~ claim 17 such that a probe comprises said extended primer having a sequence complementary to said sequence to be detected bound to said carrier macromolecule, removing any free nucleic acid not bound to said carrier macromolecule therefrom, and using the probe to detect the nucleic acid sequence in a sample by ~~hybridisation~~ hybridization thereto.

21. (Currently Amended) An immobilized nucleic acid comprising a nucleic acid linked via a covalent bond to a non-nucleotide carrier macromolecule having a molecular weight in excess of 80,000 Daltons, which the non-nucleotide carrier macromolecule is bound to a solid support.

22. (Previously Amended) A method of using the immobilized nucleic acid as claimed in claim 21 comprising:

formulating the immobilized nucleic acid as a primer or as a hybridization probe and

introducing the immobilized nucleic acid into a hybridization or amplification reaction utilizing a primer or a hybridization probe.

III. REMARKS

Preliminary Remarks

Reconsideration and allowance of the present application based on the following remarks are respectfully requested. Claims 1-22 are currently pending and remain at issue.

In paragraph 2 of the official action, the examiner objected to the informality of the term "80,000" in claims 1, 18, and 21 and suggested adding the unit of molecular weight "daltons" to the term. The applicant has amended claims 1, 18, and 31 as suggested by the examiner.

In paragraphs 3 and 5 of the official action, the examiner object to the informality of the term "macro molecule" in line 2 of claims 2, 3, and 7 and suggested amending the objected term to "macromolecule." The applicant has cancelled claim 2 without prejudice and therefore the objection to claim 2 is moot. The applicant has amended claims 3 and 7 as suggested by the examiner.

In paragraph 4 of the official action, the examiner objected to the informality of the terms "claimed claim 4" and "40,000,00" in claim 5. The examiner suggested amending these objected terms to read as "claimed in claim 4" and "4,000,000 daltons." The applicant has followed the recommendations by the examiner and amended claim 5 accordingly.

In paragraph 6 of the official action, the examiner objected to the phrase "further primer" in claims 10 and 14 and suggested amending the phrase to be directed to "another primer." The applicant has adopted the suggestion of the examiner and amended claims 10 and 14 accordingly.

In paragraph 7 of the official action, the examiner objected to the phrase "said extended primer having a sequence complementary to said sequence to be detected bound to said carrier macromolecule" in claim 20. The examiner suggested amending this phrase in claim 20 to "said extended primer has a sequence complementary to said sequence to be detected and is bound to said carrier macromolecule." The applicant has amended claim 20 as suggested by the examiner and is grateful for all of the suggested amendments to the objected claims as discussed above.

In paragraph 8 of the official action, the examiner stated this application does not contain a Brief Description of the Drawings which is required by 37 C.F.R. §1.74. In response, the applicant has submitted herewith a Brief Description of the Drawings and is supported by the specification at pages 15, lines 10 to 27. Accordingly, the Brief Description of the Drawings includes no new matter.

Amended claim 1 is directed to a process for the replication of a nucleic acid template comprising providing a primer being bonded to a carrier macromolecule having a molecular weight in excess of 80,000 daltons by hybridizing the bound primer to a template and extending said primer to form an extended primer which replicates said template in complementary form wherein said carrier macromolecule is a natural or synthetic polysaccheride, a homopolyamino acid, or a synthetic polymer having nucleophilic functional groups. Support for amended claim 1 can be found throughout the specification, for example, Example 5 and originally filed claim 2.

Amended claim 3 is directed to a process for the replication of a nucleic acid template comprising providing a primer being bonded to a carrier macromolecule having a molecular weight in excess of 80,000 daltons, hybridizing the bound primer to said template, and extending said primer to form an extended primer which replicates said template in complementary form. Support for amended claim 3 can be found throughout the specification, for example, at Example 5 and originally filed claim 1.

Amended claim 18 is directed to a method of detecting the presence of a nucleic acid bound to a non-nucleotide macromolecule comprising providing a first nucleic acid having a molecular weight in excess of 80,000 daltons, contacting said first and second nucleic acids under hybridization conditions, and detecting hybridization between said first and second nucleic acids. Support can be found throughout the specification, for example, on page 14, lines 3-25.

Amended claim 20 is directed to an immobilized nucleic acid comprising a nucleic acid linked via a covalent bond to a non-nucleotide carrier macromolecule having a molecular weight in excess of 80,000 daltons which the non-nucleotide macromolecule is bound to a solid support. Support can be found throughout the specification, for example on page 16, line 25 to page 18, line 3.

Claims 9, 11, 13, 17, 19 and 20 were amended to correct minor errors in dependency, spelling and capitalization and do not affect the patentability of these claims. Accordingly, the applicant respectfully submits consideration of these amended claims.

The applicant does not intend by these or any amendments to abandon subject matter of the claims as originally filed or later presented, and reserve the right to pursue such subject matter in continuing applications.

Patentability Remarks:

Rejection Pursuant to 35 U.S.C. §112, second paragraph, indefiniteness

In paragraphs 9-16, the examiner variously rejected claims 1-20 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

In paragraph 11 of the official action, the examiner alleged that claim 1 recited the limitation "said primer" which lacked sufficient antecedent basis. The applicant has amended claim 1 as suggested by the examiner. Claim 1 is now directed to a process for replication of a nucleic acid template comprising providing **a** primer being bonded to a carrier macromolecule having a molecular weight in excess of 80,000 Daltons, hybridizing the bound primer to said template, and extending said primer **to form an extended primer** which replicates said template in complementary form wherein said carrier macromolecule is a natural or synthetic polysaccharide, a homopolyamino acid, or a synthetic polymer having nucleophilic functional groups. Accordingly, the applicant submits amended claim one no longer lacks insufficient antecedent basis under 35 U.S.C. § 112, second paragraph.

In paragraphs 12 and 16 of the official action, the examiner rejected claims 15 and 20 under 35 U.S.C. § 112, second paragraph, for the recitation of "the extended primer," which allegedly lacked sufficient antecedent basis. In view of the foregoing amendment to claim 1 (i.e., the addition of "to form an extended primer" language), the applicant respectfully submits the rejection of claims 15 and 20 under 35 U.S.C. §112, second paragraph is now moot.

In paragraph 13 of the official action, the examiner rejected claim 17 under 35 U.S.C. §112, second paragraph for the recitation of "said biological sample," which allegedly lacked

sufficient antecedent basis in claims 1-7, 10, and 14. The examiner suggested amending claim 17 to depend from claim 16 which claims a biological sample. The applicant has amended claim 17 to depend from claim 16 as suggested by the examiner for which the applicants are grateful.

In paragraphs 14 and 15 of the official action, the examiner rejected claims 18 and 19 under 35 U.S.C. § 112, second paragraph for allegedly being indefinite. Specifically, the examiner alleged that claim 18 was directed to a method of detecting the presence of a nucleic acid bound to a carrier macromolecule but there was no carrier macromolecule in the content of the claim. The examiner further alleged that claim 19 because of its reference to the carrier macromolecule of claim 18 even though claim 18 did not contain the carrier macromolecule language. The examiner suggested adding the phrase "carrier macromolecule" into the content of claim 18. The applicant has amended claim 18 as suggested by the examiner to be directed to a method of detecting the presence of a nucleic acid bound to a non-nucleotide carrier macromolecule comprising providing a first nucleic acid bound to a carrier macromolecule having a molecular weight in excess of 80,000, providing a second nucleic acid bound to a carrier macromolecule having a molecular weight in excess of 80,000, contacting said first and second nucleic acids under hybridization conditions and detecting hybridization between said first and second nucleic acids. Claim 19 depends from claim 18 and now has a proper antecedent basis to the phrase "carrier macromolecule."

Accordingly, in view of the foregoing amendments and remarks, the applicant respectfully submits that the rejections based upon 35 U.S.C. § 112, second paragraph, of claims 1-20 is now moot and request withdrawal of the rejections.

Rejection Pursuant to 35 U.S.C. §102(b), anticipation

In paragraph 18 of the official action, the examiner rejected claims 18 and 21 under 35 U.S.C. §102(b) as being anticipated by Houtz, U.S. Patent Number 5,908,972 (hereafter Houtz). Specifically with regard to claim 18, the examiner alleged that Houtz teaches a 1056 bp-single stranded rbcMT-S cDNA hybridizes with a 2424-bp fragment in *Eco*RI digested spinach genomic DNAs, single stranded rbcMT-S cDNA probe I and a 2424-bp single stranded *Eco*RI fragment detected by the hybridization assay are first and second nucleic

acids having a molecular weight in excess of 80,000 daltons which are the same limitations as claim 18. With regard to claim 21, the examiner alleged that Houtz teaches a 876-bp *Sca*I digested fragment that is immobilized on a nylon membrane which acts as the macromolecule bound to the solid support as recited in claim 21.

In paragraph 19 of the official action, the examiner rejected claims 21 and 22 under 35 U.S.C. § 102(b) as being anticipated by Stephens *et al., J. Biol. Chem.* 266:21839-21845 (1991) (hereafter Stephens *et al.*). Specifically with regard to claim 21, the examiner alleged that Stephens *et al.* teach a 1.7-kb-single stranded C/EBP cDNA is immobilized on a nylon membrane, a 1.7-kb single stranded C/EBP cDNA acts as the macromolecule bound to a solid support as recited in claim 21. Regarding claim 22, the examiner alleged that Stephens *et al.* teach cDNA immobilized on the nylon membrane in run-on transcription assays are used as probes to hybridize with *in vitro* transcripted RNA as recited in claim 22. The applicant respectfully traverses each of these rejections in view of the claim amendments and following remarks.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *See Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628 (Fed. Cir. 1987). As amended herein, claim 18 is directed to a method of detecting the presence of a nucleic acid bound to a non-nucleotide carrier macromolecule comprising providing a first nucleic acid bound to a carrier macromolecule having a molecular weight in excess of 80,000, providing a second nucleic acid bound to a carrier macromolecule having a molecular weight in excess of 80,000, contacting said first and second nucleic acids under hybridization conditions and detecting hybridization between said first and second nucleic acids. Amended claim 21 is directed to an immobilized nucleic acid comprising a nucleic acid linked via a covalent bond to a non-nucleotide carrier macromolecule having a molecular weight in excess of 80,000, which the non-nucleotide carrier macromolecule is bound to a solid support. Amended claim 22 is dependent from claim 21.

The use of a non-nucleotide carrier macromolecule in which a covalent bound with between a nucleic acid and the non-nucleotide carrier macromolecule has a molecular weight in excess of 80,000 Daltons is novel over both Houtz and Stephens *et al.* because neither reference uses a non-nucleotide carrier macromolecule in their methods to detect the presence of a nucleic acid via hybridization. Rather the hybridization assays of Houtz and Stephens *et*

al. use single stranded nucleic acids covalently bonding to other single stranded nucleic acids that were, in some cases, immobilized to a nylon membrane. Therefore, neither Houtz nor Stephens *et al.* disclose or teach the presently claimed invention.

In view of the foregoing amendments and remarks, claims 18, 21, and 22 are not anticipated by Houtz and/or Stephens *et al.* Accordingly, the applicant submits withdrawal of this rejection.

Rejection Pursuant to 35 U.S.C. §103(a), obviousness

In paragraph 21 of the official action, the examiner rejected claims 1 and 2 under 35 U.S.C. § 103(a) as being unpatentable over Landegren *et al.*, U.S. Patent Number 4,988,617 (Landegren *et al.*) in view of Matteucci *et al.*, U.S. Patent Number 5,434,257 (hereafter Matteucci *et al.*). Specifically, the examiner alleged that it would have been *prima facie* obvious to perform the methods of claim 1 using a primer bound with a carrier macromolecule having a molecular weight in excess of 80,000 daltons in view of the patents of Landegren *et al.* and Matteucci *et al.* The examiner asserted that one would have been motivated because both Landegren *et al.* and Matteucci *et al.* have successfully used an enzyme to label a nucleic acid probe using an enzyme with a molecular weight in excess of 80,000 daltons during the process for the replication of a nucleic acid template. The applicant respectfully traverses this rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or reference when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

The examiner bears the burden of establishing a prima facie case of obviousness and "can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." *In re Fine*, 5 U.S.P.Q.2d 1598 (Fed. Cir. 1988). To support a conclusion that a claimed composition is obvious, either: (a) the

references must expressly or impliedly suggest the claimed composition to one of ordinary skill in the art, or (b) the examiner must present a convincing line of reasoning as to why a person of ordinary skill in the art would have found the claimed invention to have been obvious in light of the teachings of the references. *Ex parte Clapp*, 227 U.S.P.Q. 972, 973 (Bd. Pat. App. & Inter. 1985).

The applicants submit that Landegren *et al.* in view of Matteucci *et al.* neither teach nor suggest the applicant's claimed invention as defined by claim 1, *i.e.*, a process for the replication of a nucleic acid template comprising providing a primer being bonded to a carrier macromolecule having a molecular weight in excess of 80,000 daltons by hybridizing the bound primer to a template and extending said primer to form an extended primer which replicates said template in complementary form wherein said carrier macromolecule is a natural or synthetic polysaccheride, a homopolyamino acid, or a synthetic polymer having nucleophilic functional groups.

With respect to Landegren *et al*, the primary document, the examiner alleged since the label includes a enzyme and the enzyme is a polypeptide or protein, the enzyme taught by Landegren *et al.* is the carrier macromolecule. The applicant respectfully submits that Landegren *et al.* do not teach a carrier macromolecule that is either a natural or synthetic polysaccharide, a homopolyamino acid, or a synthetic polymer having a nucleophilic functional group exceeding a molecular weight of 80,000 daltons and is bonded to a primer for purposes of replicating a nucleic acid template. At best, Landegren *et al.* teaches a carrier macromolecule that is a polypeptide with an amino acid sequence encoding ligase which is not an element of amended claim 1. Therefore, one of skill in the art, studying the disclosure of Landegren *et al.* in view of the contradictions (use of a carrier macromolecule that is polypeptide with a heterologous amino acid sequence) would not teach or suggest a process for the replication of a nucleic acid template comprising providing a primer being bonded to a carrier macromolecule having a molecular weight in excess of 80,000 daltons by hybridizing the bound primer to a template and extending said primer to form an extended primer which replicates said template in complementary form wherein said carrier macromolecule is a natural or synthetic polysaccheride, a homopolyamino acid, or a synthetic polymer having nucleophilic functional groups.

With regard to the secondary reference, Matteucci *et al.*, the examiner cited the document for the alleged teaching that Matteucci *et al.* discloses different kinds of

compounds such as enzymes are used to covalently label nucleic acids wherein at least one of the enzymes, alkaline phosphatase, is know to have a molecular weight in excess of 80,000. The applicant submits that this secondary reference does little to overcome the failings of primary document, Landegren *et al.* Specifically, Matteucci *et al.* does not teach extending a primer that replicates a template in a complementary form with a carrier macromolecule that is a natural or syntetic polysaccharide, a homopolyamino acid or a synthetic polymer having nucleotiphilic functional groups. Rather, Matteucci *et al.* teach synthesis of oligonucleotide analogs resistant to endogenous nucleases without using any template DNA for purposes of hybridizing and targeting nucleic acids and not for replication of a nucleic acid template. In contrast, the applicant hybridizes a primer (which is bonded to a carrier macromolecule that is either a natural or synthetic polysaccharide, a homopolyamino acid, or a synthetic polymer having nucleophilic functional groups) to a template and then extending the primer to replicate the template in complementary form. Accordingly, the applicant respectfully submits one of skill in the art would not find a process for replicating a nucleic acid template using a primer bound to a carrier macromolecule using a nucleic acid template in view of Matteucci *et al.*

In summary, the applicant submits that Landegren *et al.,* either alone or in combination with Matteucci *et al.*, neither teaches nor suggest the applicant's claimed invention. Accordingly, without such teaching or suggestion, the examiner would not establish a prima facie case of obviousness. Therefore, a rejection based on 35 U.S.C. §103(a) of claim 1 should be withdrawn.

IV. CONCLUSION

In view of the foregoing, the claims are still believed to be in form for allowance, and such action is hereby solicited. If any point remains in issue which the examiner feels may be best resolved through a personal or telephone interview, the examiner is **strongly urged** to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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